ABSTRACT

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Title:

The effect of dicrocoeliosis on biotransformation of anthelmintics in mouflon

Parasitic infections can modify the host´s ability to metabolize drugs and other xenobiotics by altering the biotransformation enzymes. These changes may have various pharmacological, toxicological or physiological consequences. In our study, *in vitro* metabolism of albendazole, albendazole sulfoxide and flubendazole was tested and compared in non-infected mouflons and in mouflons infected by lancet fluke (*Dicrocoelium dendriticum*). Two groups of 5-7 years old mouflon ewes (*Ovis musimon*) were used for our study. Animals in the first group were parasitologically negative and the second group consisted of fluke positive animals. Subcellular fractions of liver homogenates from non-infected and *Dicrocoelium*-infected mouflons were isolated. The hepatic microsomal and cytosolic fractions were incubated with albendazole, albendazole sulfoxide or flubendazole. The anthelmintics and their metabolites were analyzed using HPLC. Apparent kinetic parameters (V_{max} and K_m) of biotransformation reactions were investigated and compared in non-infected mouflons and in *Dicrocoelium*-infected mouflons.

Protein concentrations in cytosolic fractions were higher in non-infected mouflons than in *Dicrocoelium*-infected mouflons. In microsomal fractions of both non-infected and infected mouflons, albendazole was metabolized through two-step S-oxidation yielding first albendazole sulfoxide followed by albendazole sulfone. Albendazole sulfoxide was converted to albendazole sulfone in microsomes. In cytosolic fractions albendazole was not oxidized. Either in microsomal or in cytosolic fractions, albendazole sulfoxide was not reduced to albendazole. In microsomal and cytosolic fractions of both non-infected and infected mouflons, flubendazole was metabolized only through reduction of carbonyl group, hydrolyzed metabolite of flubendazole was not formed. Dicrocoeliosis enhanced the formation of either albendazole sulfoxide or albendazole sulfone. Affinity of biotransformation enzymes for albendazole was significantly higher in *Dicrocoelium*-infected mouflons than in non-infected mouflons. Apparent K_m for flubendazole reduction in microsomes was also influenced by dicrocoeliosis. Affinity of reductases for flubendazole was higher in non-infected mouflons than mouflons with dicrocoeliosis.

Stereospecificity of albendazole oxidation was also affected by dicrocoeliosis. Dicrocoeliosis in mouflon increased (+)-ABZSO formation. Reduction of flubendazole is highly stereospecific in mouflon and it is not affected by dicrocoeliosis, only (+)-FLU-R was formed in both non-infected and infected mouflons.

In conclusion, dicrocoeliosis in mouflons caused only mild changes in albendazole, albendazole sulfoxide and flubendazole hepatic biotransformation. Undesirable alterations in pharmacokinetics of mentioned benzimidazole anthelmintics are not expected.